Consanguineous Marriage and the Psychopathology of Progeny: A Population-wide Data Linkage Study

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TITLE PAGE

Title: Consanguineous marriage and the psychopathology of progeny: a population-wide data-linkage study.

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Key Points

Questions: Are children of consanguineous parents at an increased risk of common mood disorder or psychoses?

Findings: This unique population-wide cohort study found a positive association between being a child of consanguineous parents and likelihood of psychotropic medication use in adulthood. Children of first cousin consanguineous parents are over three times more likely to receive medications for common mood disorders and over twice as likely to receive medications for psychoses compared to children of non-related parents.

Meaning : A child of first cousin consanguineous parents is at an increased risk of common mood disorder and psychoses.

Abstract

Importance: Approximately 1 in 10 children worldwide are born to consanguineous parents. The literature on consanguinity and mental health of progeny is scarce, even though many of the factors associated with consanguineous unions are also associated with mental health.

Objective: To determine if children of consanguineous parents are at an increased risk of common mood disorder or psychoses.

Design: A retrospective population-wide cohort study of all individuals born in Northern Ireland (NI) between 1971-1986, derived form the Child Health System Dataset, linked to nation-wide administrative data sources on prescription medication and death records.

Setting: This study was facilitated by the Honest Broker Service.

Participants: Data from the Child Health System dataset identified all 447,452 births delivered to mothers resident in NI between January 1971 and December 1986. The final dataset contained 363,960 individuals, alive and resident in NI in 2014 with full data on all variables (minus 74,738 missing HCN, 3,328 deaths and 5,426 missing data).

Exposure: Degree of parental consanguinity was determined from questions asked of the parents during routine health visitor house calls within two weeks of the child's birth.

Main Outcome(s) and Measure(s): Potential mental ill-health was determined by receipt of psychotropic medication in 2010-2014. Ever/never use was used for main analysis with sensitivity analyses using at least 3 months' prescribing. Receipt of antidepressant and/or anxiolytic medications was used as a proxy for common mood disorders, whereas receipt of antipsychotic medications was used as a proxy indicator of psychoses.

Results: Of the 363,960 individuals, 609 (0.2%) were born to consanguineous parents (CP). Multi-level logistic regression models found that children of first cousin CP were over three times as likely

to be in receipt of antidepressant and/or anxiolytic medication (OR=3.01, 95% CI 1.24, 7.31) and over twice as likely to be receipt of antipsychotic medication (OR=2.13, 95% CI 1.29, 3.51), compared to children of non-related parents after full adjustment for factors known to be associated with poor mental health.

Conclusions and Relevance: A child of consanguineous parents is at an increased risk of common mood disorder and psychoses.

Introduction

Across the world, approximately 1 in 10 children are the progeny of consanguineous parents, despite concerns over the genetic safety of such a partnership.[1] Consanguinity is defined as the union between two individuals related as second cousins or closer. The most commonly reported form of consanguineous partnership worldwide is between first cousins, who on average have co-inherited 1/8 of their genes from one or more common ancestors. First cousin offspring will therefore be homozygous at 1/16 of all loci (i.e. they will receive identical gene copies from each parent at these sites in their genome).[2,3] It is this shared genetic profile that is thought to lead to a higher prevalence of autosomal recessive disorders in children of consanguineous unions. The risk of abnormality or death in early childhood is about 5% in children of consanguineous couples compared to 2–2.5% for children of non-consanguineous couples.[4] Unsurprisingly, rates of miscarriage and stillbirth are higher amongst children of consanguineous parents.[5,6] However, some studies also suggest that consanguinity deleteriously affects late and post-pregnancy outcomes including preeclampsia, prematurity and low birthweight.[4,7] A recent report from the UK purported that in one London borough 1 in 5 of all neonatal deaths were due to their parents being related.[8] Consanguinity has also been associated with an increased risk of later life effects such as cardiovascular disease, cancer and Alzheimer's disease.[9]

However, the validity of these associations, and the magnitude of the risk, has often been contested.[10] Researchers in Australia found the risk of congenital defects in babies born to first-cousin marriages to be comparable with the risk to babies born to women aged over 40 years.[11] A recent narrative review on the effect of consanguinity on neonatal outcomes concluded that findings were inconsistent, citing poor study design and inadequate adjustment for confounding factors as the reason for observed variability.[12] And the National Society of Genetic Counsellor's in North America concluded that risks quoted from studies based on non-Western population may not be applicable to all consanguineous unions due to underlying societal differences and ethnicity-related

risk factors, suggesting that well controlled studies evaluating the effect of consanguinity have not yet been conducted.[13]

The literature on consanguinity and the mental health of progeny is scarce, despite the fact that many of the factors associated with consanguineous unions are also associated with mental health outcomes.[14–16] It is widely known that early life factors such as parental deprivation and low birth weight are associated with poor mental health outcomes in adulthood.[17,18] These factors are also associated with consanguinity.[19,20] Consanguineous pregnancies are also associated with younger maternal age which is a risk factor for poor mental health in children.[5,21] Children of consanguineous parents also face a certain degree of stigma, especially in communities where consanguinity is not the norm, and this stigma could negatively affect their mental well-being.[13] Extant studies exploring the relationship between consanguinity and mental health have been limited by study cohort size, lack of adequate controls and inconsistent measurement of mental health[15,16,22–24]. One recent study in Iran found no association between consanguinity and mental ill-health in students aged between 18 and 39 years as measured by the General Health Questionnaire (GHQ-28), however this study was based on a small sample of Medical Sciences students in one university and excluded anyone with a pre-diagnosed psychiatric disorder.[22] There is a recognised need for further study into the effect of consanguinity on late-onset disorders, such as psychoses and common mood disorders that rigorously control for potential confounding variables such as socioeconomic status, birth weight, maternal age and rural dwelling.[1]

However, it is difficult to carry out a population-wide study on the effects of consanguinity on children due to the lack of routine records on consanguineous marriage. First-cousin marriages are legal throughout the world, with the exception of the USA, North Korea and the People's Republic of China.[2] Though actual rates of consanguinity within populations are impossible to determine. It is estimated that consanguineous unions are increasing across Western Europe due to migration from areas where consanguinity is commonplace.[25,26]

Data, from Church records, are available on Roman Catholic consanguineous unions, as special dispensation is required from the church to marry. Roman Catholics hold the largest majority religion in Northern Ireland (NI) and the most recent published data in Ireland suggests 1 in 625 (0.2%) of all Roman Catholic marriages are consanguineous, which tallies with an estimated 0.1-0.2% of Roman Catholic marriages in Canada being consanguineous also.[26,27] A random survey of 630 presentations to emergency departments in NI in 1955 found 0.3% of the population to be in consanguineous unions.[28]

Aims

This paper presents the findings of a retrospective cohort study, drawing upon data from the Child Health System (CHS) dataset, which recorded information on all births in NI from 1971-1986 along with parental information, including degree of consanguinity. This unique cohort allows for the first population-wide data linkage study, linking data from the CHS dataset to primary care records, prescription medication data and death records, to determine the association between consanguinity and the long-term mental health outcomes of progeny.

Methods

Study population and design

The authors used the STROBE guidelines for reporting observational studies. Data from the Child Health System (CHS) dataset was used to form an historical cohort of all 447,452 births delivered to mothers resident in NI over the 15-year period between January 1971 and December 1986.[29,30] Details were collated on the child (including delivery method, gestational age and birth weight) from obstetric records at the time of delivery, and on the mother (including mother's age, parity and area of residence) and the father (including father's age and degree of consanguinity to the mother) by health visitors in the home typically within 1–2 weeks of the birth.[30] Health visitors are public health practitioners that provide support to all families in NI as part of our free-at-the-point-of-service

National Health Service (NHS).[31] After the introduction of the unique individual Health and Care Number (HCN) in 1998 (which replaced the previously used Community Health Index (CHI) identifier), the CHS dataset was updated allowing for direct one-to-one linkage to other contemporary health care related datasets. However not all individuals were successfully assigned a new HCN due to name changes, marriages and duplication errors. All CHS data with a HCN were linked to current population-wide data on prescription medication from the Enhanced Prescribing Database (EPD) and death records to determine the mental health profile of our cohort. The final study dataset contained 363,960 individuals born between 1971 and 1986, alive and resident in NI in 2014 with full data on all variables (Four hundred and forty seven thousand four hundred and fifty two minus 74,738 missing HCN, 3,328 deaths and 5,426 missing data) (eFigure1).

The EPD contains information on all prescriptions dispensed in community pharmacies in NI from 2010 onwards.[32] Northern Ireland's health system includes free prescription medication and means every individual is registered with a General Practitioner (GP) at birth. For this study prescribed medication was collated for the calendar years 2010-2014 inclusive.

Child Characteristics

Child gender was identified from the CHS dataset. Age was calculated as of the study mid-point (15th June 2012) and grouped as 26-29, 30-33, 34-37 and 38-41 years. Birthweight and Gestational age were used to calculate a Small for Gestational Age (SGA) variable as per the global reference for foetal weight and birthweight percentiles.[33] SGA was calculated as weighing below the 10th percentile of sex-specific, population-based birth weight reference curve for gestational age. SGA has been linked to increased risk of long-term health and social consequences such as neurocognitive impairment, hyperactivity and lower educational attainment.[34–36] Delivery method was categorised as "Natural", "Natural Assisted" and "Caesarean Section". Births were identified as singleton (n=357,351) or multiple births (n=6,609) to allow for sensitivity analyses limited to

singleton births only. Ethnicity information was not available, however at the time of the CHS less than 0.8% of the NI population was non-white.[37]

Parental Characteristics

Maternal and paternal ages were obtained from the CHS dataset. Each contained a very large age range and so only ages within three standard deviations of the mean were accepted with all others deemed at high risk of error and so placed in the "unknown" age group category. Parental age was defined as "<18 years", "18-35 years" and ">35 years," as parents under 18 years and over 35 years have been identified as being associated with a high risk of psychiatric morbidity in offspring.[38–40] Maternal parity was also identified and categorised as "first born", "par 1", "par 2" and "par 3 or more". Mothers address at birth was used to assign area-level deprivation.[41] Areas are ranked from most affluent to most deprived based on the number of households in receipt of income related state benefits and tax credits. Degree of consanguinity between the parents was based on response to questions from the Health Visitor and was identified as "non-related parents", "first cousin pairing", "second cousin pairing" and "not known".

Prescribed Medication

Receipt of psychotropic medication was used as a proxy indicator of psychopathology. Individuals were classified as being in receipt of antipsychotic medication if they received at least one prescription for antipsychotics (BNF category 4.3.6) and classified as being in receipt of medications for common mood disorders if they received at least one prescription for antidepressant medication (BNF category 4.3.4) or Anxiolytic medication (BNF category 4.3.1) over the 5 year study period (2010-2014). The BNF (British National Formulary) is the standard reference digest for medications in the UK.[42] Sensitivity analyses were carried out using a cut-off of at least three months' prescriptions, yielding similar results [eTable 1].

Data linkage

The prescribing data were linked to the CHS data using unique HCN. Linkages were undertaken by

the data custodians and the resultant research dataset containing only fully anonymised data was made available to the research team within a secure analysis environment. Individual-level informed consent was not required as only non-identifiable data was made available to the research team. Ethical approval was obtained from the Office for Research Ethics Committees Northern Ireland (ORECNI).

Analytic approach

Analysis was divided into three stages. First, descriptive analysis of the cohort aimed to determine the demographic profile of children born to consanguineous partnerships. Second, multi-level, multivariable regression models were constructed to determine the likelihood of medication for common mood disorders given degree of consanguinity between the parents, adjusting for factors known to be associated with mental ill-health and multi-level adjustment for the natural clustering of individuals within GP Practices. Receipt of antidepressant and/or anxiolytic medication was used as a proxy indicator of common mood disorder. This method has been validated in previous studies.[43,44] Due to small numbers in each of the consanguinity categories measures of area deprivation and area rurality were added to the multi-level models separately to ensure convergence. Third, as per the method above, multi-level, multivariable regression models were constructed to determine the likelihood of psychotropic medication given degree of parental consanguinity. Receipt of psychotropic medication was used as a proxy measure of psychoses.[32] Sensitivity analyses were carried out repeating each of the multi-level regression analyses limited to singleton births only (n= 357,351) yielding similar results.

Missing HCN

A total of 74,738 (16.7%) individuals were not included in the cohort as they were unable to be assigned a HCN when the unique identifier was updated from CHI to HCN. A CHI to HCN 'look-up' was created matching individuals on name, address and date of birth, and allowing a present HCN to be assigned to the historic Child Health System dataset. Individuals with incomplete data in these

fields may not have been successfully assigned a HCN. The HCN indicator was used to link the CHS with the EPD dataset. This proportion of the population was further explored to assess whether it varied significantly from the study cohort. Female gender (OR=1.35, 95% CI 1.33, 1.37) was associated with missing HCN, likely due to marital name changes or migration since assignment of original CHI number. Older age (OR=3.09, 95% CI 3.01, 3.17 for 38-41 years compared to 26-30 years), being SGA (OR=1.88, 95% CI 1.83, 1.93) and having first cousin consanguineous parents (OR=1.74, 95% CI 1.35, 2.25) were also associated with missing HCN likely due to the higher mortality risk in this group [eTable 2].

Results

Of the 363,960 individuals born 1971-1986 in our cohort (52.5% male), 609 (0.2%) were born to consanguineous parents (CP); 349 to second cousin CP and 260 to first cousin CP (see Table 1).

(Table 1 about here)

There was no significant difference between the gender distribution of offspring of CP, however, a larger proportion of consanguineous offspring were younger with 43.1% of the first cousin consanguineous parents group aged 26-29 years compared to just 27.1% of the non-related parents group. There was no significant difference in SGA and delivery method in consanguineous offspring versus non-consanguineous offspring, but consanguineous offspring did tend to come from larger families with almost half (45.9%) of children of first cousins being 3rd born or greater. Father's age was also greater in first cousin consanguineous unions (mean age 37.4 years) compared to non-related parents (mean age 30.1 years). A greater proportion of consanguineous offspring were from deprived and rural areas.

There was a clear stepwise increase in the proportion of consanguineous offspring in receipt of psychotropic medication with degree of consanguinity. Over a third (35.8%) of children of first

cousin consanguineous unions were in receipt of antidepressant and/or anxiolytic medication compared to just over a quarter (26.0%) of non-related offspring. And 8.5% of first cousin CP offspring were in receipt of antipsychotic medication compared to 4.3% of second cousin CP offspring and 2.7% of non-related offspring.

In the multi-level regression models, being female (OR=1.79, 95% CI 1.72, 1.88), middle-aged (OR=1.11, 95% CI 1.04, 1.19 for 38-41 year olds compared to 26-30 year olds) or from a deprived area (OR=1.10, 95% CI 1.04, 1.15 for deprived compared to non-deprived areas) was associated with an increased likelihood of being in receipt of medications for common mood disorders, whilst being from a rural area was associated with a decreased likelihood of medication (OR=0.91, 95% CI 0.85 ,0.97) (see Table 2). These figures reflect well established associations between sociodemographic factors and mental ill-health and affirm the robustness of prescribed antidepressant and/or anxiolytic medication as a measure of common mood disorder. There was a clear stepwise increase in the odds ratios for antidepressant and/or anxiolytic medication given degree of consanguinity of parents. Children of first cousin CP were over three times more likely to be in receipt of medications for common mood disorders compared to children of non-related parents (OR=3.01, 95% CI 1.24, 7.31), after full adjustment for factors known to be associated with poor mental health. The association between being a child of second cousin CP and medications for common mood disorders was elevated but not statistically significant at the conventional 5% level (OR=1.31, 95% CI 0.63, 2.71). Restricting analysis to singleton births did not affect these associations (OR=3.01 (95% CI 1.23, 7.41) first cousin & OR=1.31 (95% CI 0.63, 2.71) for second cousin) [full sensitivity results available eTable 3].

(Table 2 about here)

Table 3 shows the results of the multi-level models investigating the association between antipsychotic medication and consanguinity of parents. Being older (OR=1.15, 95% CI 1.08, 1.23 for 38-41 year olds compared to 26-30 year olds), greater than fourth born (OR=1.15, 95% CI 1.07, 1.23

for par 3 or more compared to first born) or from a deprived area (OR=1.34, 95% CI 1.28, 1.41 for deprived compared to non-deprived areas) was associated with an increased likelihood of being in receipt of antipsychotic medication, whilst being female (OR=0.57, 95% CI 0.55 ,0.60) and from rural areas (OR=0.92, 95% CI 0.85, 0.99 for rural compared to urban) was associated with a decreased likelihood of antipsychotic medication. Children of first cousin CP were over twice as likely to be in receipt of antipsychotic medication compared to children of non-related parents (OR=2.13, 95% CI 1.29, 3.51), after full adjustment for factors known to be associated with poor mental health. Restricting analysis to singleton births did not affect these associations (OR=2.19 (95% CI 1.32, 3.61) first cousin & OR=1.37 (95% CI 0.78, 2.40) for second cousin) [full sensitivity results available eTable4].

Table 3 (about here)

Risk of psychotropic medication was also elevated in children of second cousin CP, but was not statistically significant at the conventional 5% level (OR=1.37, 95% CI 0.79, 2.40). Likelihood Ratio tests for interactions found no interaction between rurality and consanguinity (chi2 = 6.37, p=0.3827) or deprivation and consanguinity (chi2 = 7.99, p=0.6298).

Discussion

This study clearly shows that a child of first cousin consanguineous parents (CP) is at an increased risk of common mood disorder and psychoses. In the study population 0.2% of children were born to CP, which is consistent with previous estimates of population consanguinity in Ireland and amongst Roman Catholic populations.[26–28] Female gender, middle-age and deprivation was associated with receipt of antidepressant and/or anxiolytic medication validating this measure, as these factors are known in the literature to be associated with risk of depression and anxiety disorders.[45,46] Children of first cousin CP were over three times as likely be in receipt of medication

for common mood disorders compared to children of non-related parents. In addition, children of first cousin CP were over twice as likely be in receipt of antipsychotic medication compared to children of non-related parents. With male gender, older age, deprivation, birthweight (SGA) and parity all also significantly associated with antipsychotic risk validating this measure further as these factors are known to be associated with risk of psychoses.[18,47,48]

There are a number of theories as to why consanguinity may result in mental ill-health in progeny. High heritability points to a major role for inherited genetic variants in the aetiology of psychiatric disorders.[49] In recent years, genome-wide association studies (GWAS) of schizophrenia, bipolar disorder and major depression have provided strong support for a substantial polygenic contribution of a large number of small genetic effects.[50,51] An alternative view is that most of the variance for certain complex diseases is due to moderately highly penetrant rare variants.[53] Consanguinity as a form of assortative mating , increases polygenic loading and therefore is likely associated with a higher risk of mental disorder in progeny.[52] This is only true however, if each of the parents carry common susceptibility loci.

A second theory suggests that having CP is associated with "social stigma", especially in Western societies where consanguineous partnerships are considered taboo.[13] Being a member of a minority population and even perceived discrimination is known to be associated with poor mental health outcomes.[54,55] However, it is not known how many of the children in our cohort were aware of the genetic relationship of their parents.

Thirdly, the observed association may be due to some unmeasured confounding relating to both the likelihood of consanguinity and to decreased mental health. However, the study design allowed for a robust examination of the mental health risk associated with CP: the data was population-wide, capturing an entire cohort born over 15 years and contained detailed neonatal information on the individual and detailed sociodemographic information on the parents. The prevalence of CP recorded in this study is in keeping with other estimates and the associations between mental health

and a range of sociodemographic factors reflect those found in other studies worldwide. The analysis included regression modelling adjusting for a range of confounders known to be associated with mental health and multi-level modelling allowed for excellent adjustment of the potential unknown confounding associated with the natural clustering of individuals within GP Practices. The results illustrate a clear increasing, step-wise relationship between level of consanguinity and mental ill-health suggesting a quasi-dose-response relationship, supporting a causal association between CP and mental health of progeny.

This study has significant strengths and limitations. Its strengths; it is the first ever population-wide study of consanguinity and mental health of progeny and it uses an objective measure of mental ill-health in the form of prescribed medication data. Its caveats, concern the information limitations of the data, including prescription data which does not include diagnosis codes or indication for use. However, prescription medication as an indicator of mental ill-health has been used effectively in previous studies worldwide.[44,56–58] Consanguinity was identified by parents' response to a question asked by a Health Visitor in their home, but some individuals may not have identified themselves as CP due to fears of stigma, discrimination and even legal prosecution.[13] However, there is no legal impairment to consanguinity in NI, so fear of legal prosecution is unlikely to be a factor. There is no information on the mental health of the parents of our cohort. Parental mental health is known to be related to the mental health of the children; however, almost all consanguineous parents would have had to suffer from poor mental health themselves to produce the effects observed in this study, and there is no evidence to suggest poorer mental health amongst consanguineous couples. Lastly, in order to experience the outcome of interest participants must be alive during 2010-2014. However, psychopathology is known to be associated with mortality risk meaning there is mortality bias in our results. This likely excludes those with the most severe mental disorders, biasing results towards the null, but does not affect the robustness of the observed associations.

Conclusion

In conclusion, despite the recent debate around the physical genetic risk of CP, more research is required into the psychological effects of CP on progeny. This study suggests a significant impact of consanguinity on mental health independent of parental age, mother's parity, birthweight, deprivation and rurality. However, in order to effectively analyse the effect of consanguinity on physical and mental ill-health there is a need to implement accurate record keeping of cousin-marriage. This study demonstrates the ability of population-wide data linkage to explore hard to reach populations and would call upon other countries with similar large-scale administrative data sources to utilise their data to explore the effects of consanguinity on offspring. The authors suggest these findings will be of value to health promotion and public health professionals, and to those commissioning antenatal, paediatric, and clinical genetic services. Sensitive advice about the risks should be provided to communities who favour consanguineous unions to assist in reproductive decision making.

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Table 1: Proportion of the population with consanguineous parents (CP) by level of consanguinity and demographic characteristics

		All N=363,960	% Not related (n=344,183)	% Second Cousins (n=349)	% First Cousins (n=260)	% Not Known (n=19,168)	*p**
Gender	**Male**	191,102 (52.5)	52.5	51.3	53.9	51.7	0.820
	Female	172,858 (47.5)	47.5	48.7	46.1	48.3	
Age (years)	**26-29**	97,399 (26.8)	27.1	39.8	43.1	21.1	<0.01
	30-33	95,663 (26.3)	26.4	21.2	18.1	24.3	
	34-37	87,065 (23.9)	23.0	17.5	22.3	40.5	
	38-41	83,833 (23.0)	23.5	21.5	16.5	14.1	
SGA	**No**	342,412 (94.1)	94.1	93.7	92.3	93.8	0.450
	Yes	21,548 (5.9)	5.9	6.3	7.7	6.2	
Delivery Method	**Natural**	290,841 (79.9)	80.0	78.2	82.3	79.0	0.460
	Other	73,119 (20.1)	20.0	21.8	17.7	20.1	
Parity	**First Born**	96,685 (26.6)	26.5	27.8	20.0	27.9	<0.01
	1	105,750 (29.1)	29.3	22.6	23.5	25.8	
	2	64,794 (17.8)	17.9	16.1	12.7	16.0	
	>3	70,968 (19.5)	19.5	22.4	33.5	19.7	
	Unknown	25,763 (7.1)	6.9	11.2	10.4	10.6	
Mother's Age	**Mean (years)**	27.7	27.7	27.0	27.0	27.3	0.077
Father's Age	**Mean (years)**	30.2	30.1	35.2	37.4	31.6	<0.01
Deprivation at Birth	**Not deprived**	200,238 (55.0)	55.4	58.7	41.9	48.0	<0.01
	Deprived	156,797 (43.1)	42.7	38.4	53.1	49.8	
	Not Known	6,925 (1.9)	1.9	2.9	5.0	2.2	
Rurality at Birth	**Not rural**	144,647 (39.7)	39.8	22.4	31.2	39.2	<0.01
	Rural	212,369 (58.4)	58.3	74.8	63.9	58.6	
	Not Known	6,944 (1.9)	1.9	2.9	5.0	2.2	
Common Mood Medication	**No**	269,201 (74.0)	74.0	68.8	64.2	73.2	<0.01
	Yes	94,759 (26.0)	26.0	31.2	35.8	26.8	
Antipsychotic Medication	**No**	354,156 (97.3)	97.3	95.7	91.5	96.9	<0.01
	Yes	9,804 (2.7)	2.7	4.3	8.5	3.1	

**p represents chi^2 test for difference between not related and related populations only (excluding 'not known')*

Table 2: Multi-level regression models to determine the likelihood of antidepressant and/or anxiolytic medication given parental consanguinity, adjusting for the clustering of individuals within GP practices. Figures represent Odds Ratios (95% Confidence Intervals)

		Unadjusted	Model 1	Model 2
Consanguineous Parents	**No** **First Cousins** **Second Cousins** **Not Known**	1.00 3.01 (1.24,7.31) 1.32 (0.64,2.72) 1.03 (0.94,1.14)	1.00 2.99 (1.23,7.27) 1.30 (0.63,2.70) 1.00 (0.90,1.10)	1.00 3.01 (1.24,7.31) 1.31 (0.63,2.71) 1.00 (0.90,1.10)
Gender	**Male** **Female**		1.00 1.79 (1.72,1.88)	1.00 1.79 (1.71,1.87)
Age (years)	**26-29** **30-33** **34-37** **38-41**		1.00 1.05 (0.99,1.12) 1.10 (1.03,1.17) 1.11 (1.04,1.19)	1.00 1.05 (0.99,1.12) 1.09 (1.02,1.17) 1.11 (1.04,1.19)
SGA	**No** **Yes**		1.00 1.06 (0.97,1.16)	1.00 1.06 (0.97,1.17)
Delivery Method	**Natural** **Natural Assisted** **C-section**		1.00 1.03 (0.95,1.10) 0.97 (0.89,1.06)	1.00 1.02 (0.95,1.10) 0.97 (0.89,1.05)
Parity	**First Born** **1** **2** **>3** **Unknown**		1.00 0.97 (0.91,1.04) 0.93 (0.87,1.00) 1.00 (0.93,1.07) 0.93 (0.84,1.03)	1.00 0.97 (0.92,1.04) 0.93 (0.87,1.00) 1.01 (0.94,1.09) 0.93 (0.84,1.04)
Mother's Age	**<18** **18-35** **>35** **Not known**		1.06 (0.85,1.33) 1.00 1.01 (0.92,1.10) 1.05 (0.67,1.64)	1.04 (0.86,1.34) 1.00 1.00 (0.92,1.10) 1.04 (0.67,1.63)
Father's Age	**<18** **18-35** **>35** **Not known**		1.90 (0.86,4.21) 1.00 0.93 (0.86,1.00)	1.91 (0.87,4.23) 1.00 0.93 (0.86,1.00)

			1.11 (1.02,1.20)	1.12 (1.03,1.22)
Deprivation at Birth	**Not Deprived** **Deprived** **Not known**		1.00 1.10 (1.04,1.15) 0.88 (0.73,1.04)	- - -
Urbanicity at Birth	**Urban** **Rural** **Not known**		- - -	1.00 0.91 (0.85,0.97) 0.79 (0.65,0.94)
Variance		0.3527591	0.3518419	0.3529185
p		<0.001	<0.001	<0.001
VPC		0.097	0.097	0.097

Table 3: Multi-level regression models to determine the likelihood of antipsychotic medication given parental consanguinity, adjusting for the clustering of individuals within GP practices. Figures represent Odds Ratios (95% Confidence Intervals)

		Unadjusted	**Model 1**	**Model 2**
Consanguineous Parents	**No** **First Cousins** **Second Cousins** **Not Known**	1.00 2.30 (1.40,3.77) 1.39 (0.80,2.42) 0.97 (0.89,1.06)	1.00 2.09 (1.26,3.44) 1.39 (0.79,2.43) 0.92 (0.84,1.01)	1.00 2.13 (1.29,3.51) 1.37 (0.79,2.40) 0.92 (0.84,1.01)
Gender	**Male** **Female**		1.00 0.57 (0.55,0.60)	1.00 0.57 (0.55,0.60)
Age (years)	**26-29** **30-33** **34-37** **38-41**		1.00 1.04 (0.98,1.11) 1.10 (1.03,1.17) 1.15 (1.08,1.23)	1.00 1.04 (0.98,1.11) 1.10 (1.03,1.17) 1.15 (1.08,1.22)
SGA	**No** **Yes**		1.00 1.16 (1.07,1.26)	1.00 1.18 (1.09,1.28)
Delivery Method	**Natural** **Natural** **Assisted**		1.00 1.04 (0.97,1.11)	1.00 1.03 (0.96,1.10)

	C-section		1.09 (1.01,1.18)	1.08 (1.00,1.17)
Parity	**First Born** **1** **2** **>3** **Unknown**		1.00 1.04 (0.98,1.11) 1.08 (1.00,1.15) 1.15 (1.07,1.23) 1.03 (0.93,1.13)	1.00 1.05 (0.98,1.11) 1.08 (1.01,1.16) 1.18 (1.10,1.26) 1.03 (0.93,1.14)
Mother's Age	**<18** **18-35** **>35** **Not known**		1.12 (0.93,1.35) 1.00 0.98 (0.90,1.06) 0.90 (0.60,1.35)	1.15 (0.96,1.39) 1.00 0.97 (0.90,1.05) 0.88 (0.59,1.33)
Father's Age	**<18** **18-35** **>35** **Not known**		1.43 (0.84,2.42) 1.00 1.02 (0.95,1.10) 1.32 (1.23,1.42)	1.45 (0.85,2.47) 1.00 1.01 (0.94,1.09) 1.35 (1.26,1.45)
Deprivation at Birth	**Not Deprived** **Deprived** **Not known**		1.00 1.34 (1.28,1.41) 1.13 (0.94,1.35)	- - -
Urbanicity at Birth	**Urban** **Rural** **Not known**		- - -	1.00 0.92 (0.85,0.99) 0.89 (0.74,1.07)
Variance		0.354988	0.3183298	0.3488054
p		<0.001	<0.001	<0.001
VPC		0.097	0.088	0.096

Online Only Tables

eTable 1: Multi-level regression models to determine the likelihood of ≥3 months' antidepressant and/or anxiolytic or ≥3 months' antipsychotic medication prescriptions given parental consanguinity, adjusting for the clustering of individuals within GP practices. Figures represent Odds Ratios (95% Confidence Intervals)

		CMD ≥3		AP≥3	
		Model 1	**Model 2**	**Model 1**	**Model 2**
Parents Related	**Not related**	1.00	1.00	1.00	1.00
	First cousins	1.99 (1.27,3.12)	2.01 (1.28,3.15)	1.98 (1.04,3.77)	2.03 (1.07,3.85)
	Second cousins	1.06 (0.73,1.54)	1.06 (0.73,1.54)	1.83 (0.94,3.55)	1.82 (0.94,3.52)
	Not known	0.98 (0.92,1.03)	0.98 (0.92,1.03)	0.95 (0.84,1.07)	0.95 (0.84,1.08)
Gender	**Male**	1.00	1.00	1.00	1.00
	Female	1.47 (1.43,1.50)	1.46 (1.42,1.50)	0.49 (0.46,0.52)	0.49 (0.46,0.52)
Age (years)	**26-29**	1.00	1.00	1.00	1.00
	30-33	1.16 (1.12,1.21)	1.16 (1.12,1.21)	1.12 (1.03,1.22)	1.12 (1.03,1.22)
	34-37	1.34 (1.29,1.39)	1.34 (1.29,1.39)	1.22 (1.12,1.33)	1.22 (1.12,1.33)
	38-41	1.44 (1.39,1.50)	1.44 (1.39,1.49)	1.45 (1.33,1.58)	1.45 (1.33,1.57)
SGA	**No**	1.00	1.00	1.00	1.00
	Yes	1.11 (1.06,1.16)	1.12 (1.06,1.17)	1.25 (1.13,1.39)	1.27 (1.15,1.41)
Delivery Method	**Natural**	1.00	1.00	1.00	1.00
	Assisted	1.02 (0.98,1.06)	1.02 (0.97,1.06)	1.03 (0.94,1.13)	1.02 (0.93,1.11)
Parity	**First Born**	1.00	1.00	1.00	1.00
	1	0.97 (0.94,1.01)	0.97 (0.94,1.01)	1.06 (0.97,1.14)	1.06 (0.98,1.15)
	2	0.97 (0.93,1.01)	0.97 (0.94,1.01)	1.08 (0.99,1.18)	1.09 (1.00,1.19)
	>3	1.02 (0.97,1.06)	1.03 (0.99,1.07)	1.18 (1.08,1.29)	1.22 (1.11,1.33)
	Unknown	0.92 (0.87,0.98)	0.92 (0.87,0.98)	1.04 (0.90,1.19)	1.04 (0.91,1.19)
Mother's Age	**<18**	1.09 (0.97,1.22)	1.10 (0.98,1.24)	1.26 (1.00,1.60)	1.30 (1.02,1.64)
	18-35	1.00	1.00	1.00	1.00
	>35	0.99 (0.94,1.04)	0.98 (0.93,1.04)	1.02 (0.91,1.13)	1.01 (0.90,1.13)
	Not known	0.88 (0.69,1.13)	0.88 (0.69,1.13)	1.03 (0.62,1.70)	1.01 (0.61,1.67)
Father's Age	**<18**	1.22 (0.85,1.77)	1.24 (0.86,1.79)	1.19 (0.57,2.46)	1.21 (0.58,2.51)
	18-35	1.00	1.00	1.00	1.00
	>35	0.97 (0.93,1.01)	0.97 (0.93,1.01)	1.08 (0.99,1.19)	1.07 (0.97,1.17)
	Not known	1.10 (1.05,1.15)	1.12 (1.07,1.17)	1.28 (1.17,1.40)	1.31 (1.19,1.44)
Deprivation at Birth	**Not Deprived**	1.00	-	1.00	
	Deprived	1.14 (1.11,1.18)	-	1.35 (1.27,1.44))	
Urbanicity at Birth	**Urban**	-	1.00		1.00
	Rural	-	0.91 (0.87,0.95)		0.93 (0.85,1.01)
Variance		0.159565	0.1584288	0.2210672	0.2385557
p		<0.001	<0.001	<0.001	<0.001
VPC		0.046	0.046	0.063	0.068

eTable 2: Regression analysis to determine likelihood of missing HCN given neonatal factors and consanguinity of parents

		Model 1
Consanguineous Parents	**No**	1.00
	First Cousins	1.74 (1.35,2.25)
	Second Cousins	1.18 (0.92,1.52)
	Not Known	1.72 (1.67,1.77)
Gender	**Male**	1.00
	Female	1.35 (1.33,1.37)
Age (years)	**26-29**	1.00
	30-33	1.27 (1.23,1.31)
	34-37	1.53 (1.50,1.58)
	38-41	3.09 (3.02,3.17)
SGA	**No**	1.00
	Yes	1.89 (1.83,1.93)
Delivery Method	**Natural**	1.00
	Other	1.06 (1.04,1.08)
Parity	**First Born**	1.00
	1	0.85 (0.83,0.87)
	2	0.78 (0.76,0.80)
	>3	0.75 (0.73,0.76)
	Unknown	1.26 (1.22,1.31)

eTable 3: Multi-level regression models to determine the likelihood of antidepressant and/or anxiolytic medication given parental consanguinity for singleton births only, adjusting for the clustering of individuals within GP practices. Figures represent Odds Ratios (95% Confidence Intervals)

		Unadjusted	Model 1	Model 2
Consanguineous Parents	**No** **First Cousins** **Second Cousins** **Not Known**	1.00 3.00 (1.22,7.36) 1.32 (0.64,2.72) 1.02 (0.92,1.13)	1.00 3.00 (1.22,7.38) 1.30 (0.63,2.70) 0.98 (0.89,1.09)	1.00 3.01 (1.23,7.41) 1.31 (0.63,2.71) 0.98 (0.89,1.09)
Gender	**Male** **Female**		1.00 1.79 (1.71,1.87)	1.00 1.78 (1.70,1.86)
Age (years)	**26-29** **30-33** **34-37** **38-41**		1.00 1.06 (0.99,1.13) 1.10 (1.03,1.18) 1.12 (1.05,1.19)	1.00 1.06 (0.99,1.13) 1.10 (1.03,1.17) 1.11 (1.04,1.19)
SGA	**No** **Yes**		1.00 1.07 (0.98,1.18)	1.00 1.08 (0.98,1.19)
Delivery Method	**Natural** **Natural** **Assisted** **C-section**		1.00 1.04 (0.97,1.12) 0.98 (0.90,1.07)	1.00 1.04 (0.96,1.12) 0.98 (0.90,1.07)
Parity	**First Born** **1** **2** **>3** **Unknown**		1.00 0.98 (0.92,1.05) 0.94 (0.88,1.01) 1.00 (0.93,1.08) 0.94 (0.84,1.04)	1.00 0.98 (0.92,1.05) 0.95 (0.88,1.02) 1.02 (0.94,1.10) 0.94 (0.85,1.04)
Mother's Age	**<18** **18-35** **>35** **Not known**		1.06 (0.85,1.33) 1.00 0.99 (0.91,1.09) 1.05 (0.67,1.65)	1.07 (0.86,1.34) 1.00 0.99 (0.90,1.09) 1.04 (0.67,1.64)
Father's Age	**<18** **18-35** **>35** **Not known**		1.90 (0.86,4.21)	1.92 (0.87,4.24)

			1.00 0.93 (0.87,1.01) 1.11 (1.02,1.20)	1.00 0.93 (0.86,1.01) 1.12 (1.03,1.22)
Deprivation at Birth	**Not Deprived** **Deprived** **Not known**		1.00 1.10 (1.04,1.15) 0.87 (0.73,1.05)	- - -
Urbanicity at Birth	**Urban** **Rural** **Not known**		- - -	1.00 0.91 (0.86,0.97) 0.79 (0.65,0.94)
Variance		0.3550799	0.3542844	0.3554447
p		<0.001	<0.001	<0.001
VPC		0.100	0.097	0.098

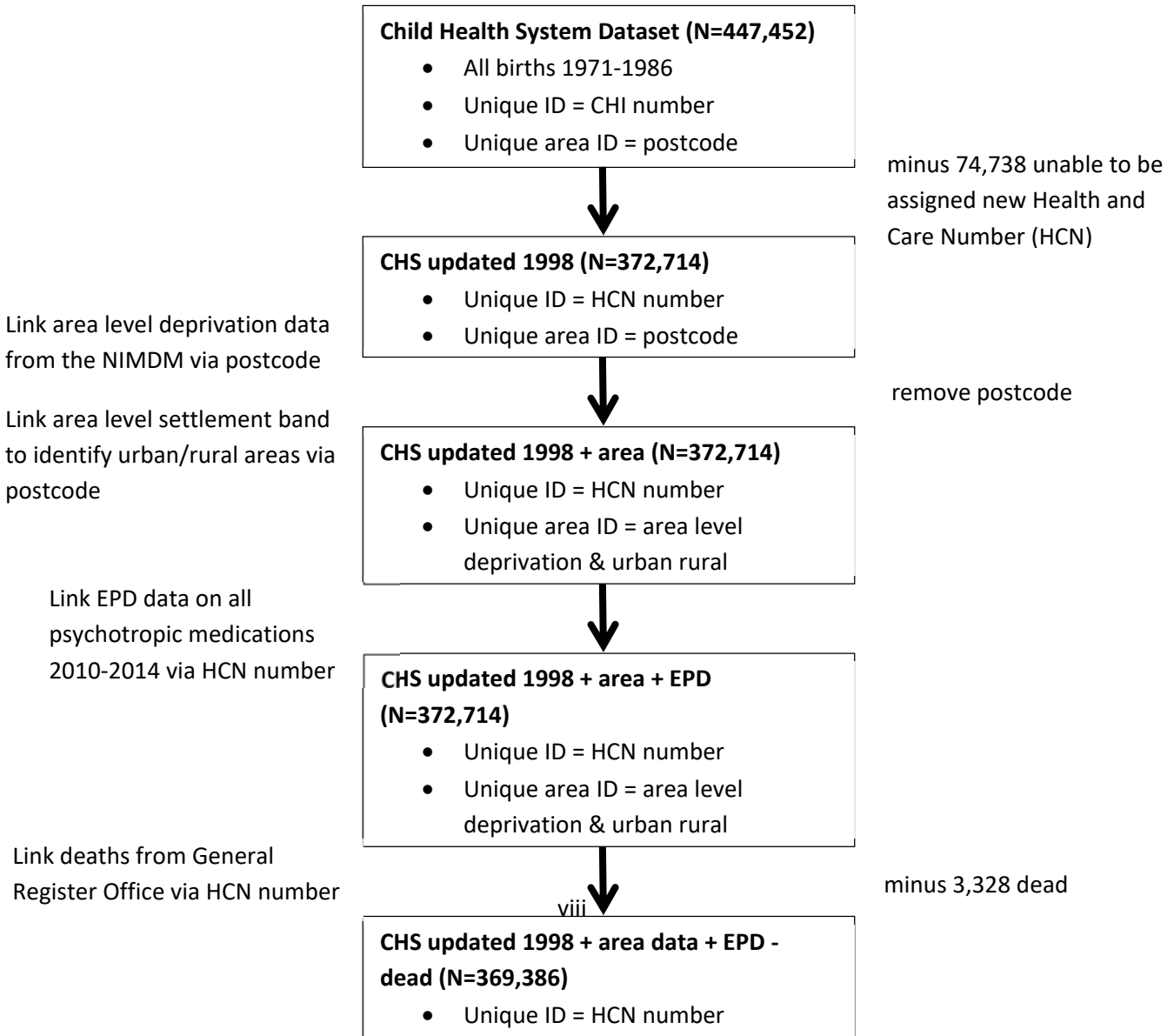
eTable 4: Multi-level regression models to determine the likelihood of antipsychotic medication given parental consanguinity for singleton births only, adjusting for the clustering of individuals within GP practices. Figures represent Odds Ratios (95% Confidence Intervals)

		Unadjusted	Model 1	Model 2
Consanguineous Parents	**No**	1.00	1.00	1.00
	First Cousins	2.37	2.13	2.19
		(1.44,3.89)	(1.29,3.53)	(1.32,3.61)
	Second Cousins	1.39	1.38	1.37
		(0.80,2.41)	(0.79,2.42)	(0.78,2.40)
	Not Known	0.97	0.92	0.92
		(0.89,1.07)	(0.84,1.01)	(0.84,1.01)
Gender	**Male**		1.00	1.00
	Female		0.57	0.57
			(0.55,0.60)	(0.55,0.60)
Age (years)	**26-29**		1.00	1.00
	30-33		1.04	1.04
			(0.98,1.11)	(0.98,1.11)
	34-37		1.10	1.10
			(1.03,1.17)	(1.03,1.17)
	38-41		1.15	1.14
			(1.08,1.22)	(1.07,1.22)
SGA	**No**		1.00	1.00
	Yes		1.18	1.20
			(1.09,1.28)	(1.11,1.30)
Delivery Method	**Natural**		1.00	1.00
	Natural Assisted		1.04	1.03
			(0.97,1.12)	(0.96,1.11)
	C-section		1.09	1.08
			(1.00,1.18)	(1.00,1.17)
Parity	**First Born**		1.00	1.00
	1		1.05	1.05
			(0.99,1.12)	(0.99,1.12)
	2		1.08	1.09
			(1.01,1.16)	(1.02,1.17)
	>3		1.16	1.18
			(1.08,1.24)	(1.10,1.27)
	Unknown		1.03	1.03
			(0.93,1.14)	(0.94,1.14)
Mother's Age	**<18**		1.12	1.14
			(0.93,1.35)	(0.95,1.38)
	18-35		1.00	1.00
	>35		0.97	0.97
			(0.89,1.06)	(0.89,1.05)
	Not known		0.90	0.89
			(0.60,1.36)	(0.59,1.34)
Father's Age	**<18**		1.44	1.47
			(0.85,2.45)	(0.86,2.50)
	18-35		1.00	1.00
	>35		1.02	1.01
	Not known		(0.94,1.09)	(0.93,1.08)

			1.32 (1.23,1.42)	1.35 (1.25,1.44)
Deprivation at Birth	**Not Deprived** **Deprived** **Not known**		1.00 1.34 (1.28,1.41) 1.10 (0.92,1.33)	- - -
Urbanicity at Birth	**Urban** **Rural** **Not known**		- - -	1.00 0.92 (0.86,0.99) 0.88 (0.72,1.06)
Variance		0.3562542	0.3519837	0.350317
p		<0.001	<0.001	<0.001
VPC		0.098	0.097	0.096

Online Only Figures

eFigure 1: Flow-chart illustrating the generation of the study dataset


Child Health System Dataset (N=447,452)
All births 1971-1986
Unique ID = CHI number
Unique area ID = postcode
minus 74,738 unable to be assigned new Health and Care Number (HCN)
CHS updated 1998 (N=372,714)
Unique ID = HCN number
Unique area ID = postcode
Link area level deprivation data from the NIMDM via postcode
remove postcode
Link area level settlement band to identify urban/rural areas via postcode
CHS updated 1998 + area (N=372,714)
Unique ID = HCN number
Unique area ID = area level deprivation & urban rural
Link EPD data on all psychotropic medications 2010-2014 via HCN number
CHS updated 1998 + area + EPD (N=372,714)
Unique ID = HCN number
Unique area ID = area level deprivation & urban rural
Link deaths from General Register Office via HCN number
minus 3,328 dead
viii
CHS updated 1998 + area data + EPD - dead (N=369,386)
Unique ID = HCN number

eFigure 1: Flow-chart illustrating the generation of the study dataset